Automated Adverse Respiratory Event Detection in Volunteers Receiving Opioid Analgesics

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Abstract:

Introduction: The underlying problem for two of the three most common patterns of unexpected hospital deaths (PUHD) is hypoventilation[1]. Concern over this opioid-induced respiratory depression has led many experts and consensus guidelines to recommend that all patients receiving opioids be monitored for respiration. We propose an additional metric, ataxic breathing severity, be monitored in patients receiving opioids. Methods: With IRB approval, data were collected from 26 volunteers who were administered target controlled infusions of remifentanil and propofol in order to induce low respiratory rates. Data were collected from a suite of sensors which were analyzed using a single, custom breath detection algorithm. Three domain experts rated the data according to degree of irregularity, or ataxia, in the respiratory waveform. A machine learning algorithm was then trained to reproduce those results. Results: Interrater reliability analysis confirmed that a machine learning algorithm was capable of mimicking scores from domain experts with a high degree of accuracy. Conclusion: Detecting ataxic, or irregular, respiratory rate is possible using an automated detection system.

INTRODUCTION & BACKGROUND

Respiratory depression is the most likely mechanism underlying the high morbidity and mortality rates associated with opioid use, both legitimate and illicit[2-4]. A recent analysis of the Anesthesia Closed Claims Project database found that in 92 respiratory depression related cases, “the vast majority of events occurred within 24 hours of surgery and 97% were preventable with better monitoring and response” [4].

These problems would be especially troublesome during long-range, manned space missions where monitoring personnel are limited due to either sedation of crew members or an injury rendering the crew short-handed.

Respiratory depression is caused by drug-induced inhibition of the breathing control center of the brain stem. Partial to full airway obstruction is an anatomic problem involving the soft palate, tongue base, and/or epiglottis, caused by drug-induced decreases in airway patency and muscle tone. Sedatives and opioids depress the response to elevated CO_2 (reduced drive to breathe), worsen arousal, cause airway obstruction, and change sleep patterns[6-10]

These adverse respiratory effects often appear quickly following opioid administration, and may lead to adverse problems such as central and obstructive apneas/hypopneas, ataxic breathing and hypoxemia, which frequently develop without underlying cardiopulmonary disease[3].

Monitoring for these effects in the perioperative period typically includes measurement of arterial oxygen saturation by pulse oximetry (SpO_2), respiratory rate,

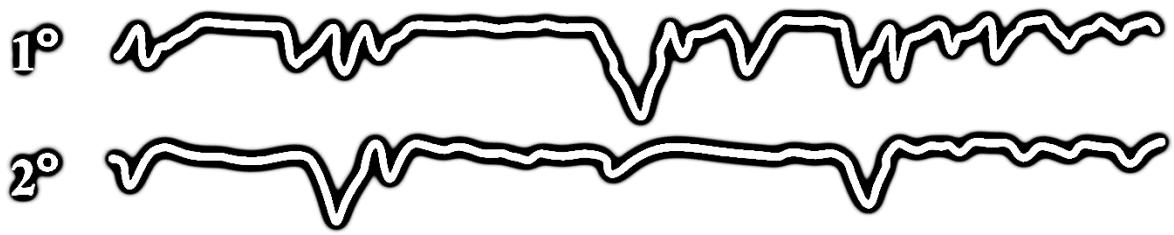

Figure 1: Biot's "ataxic" breathing in a 16 year old male with tuberculosis meningitis. The waveforms depict an irregular respiration pattern from a spirometer.

end-tidal carbon dioxide ($P_{et}CO_2$.) by capnometry, and systematic sedation assessments[11-13]. However, slow response time, high equipment costs, and unreliability of human factors limit the effectiveness of these monitoring methods, respectively[13,14].

As early as 1876, French physician Chamille Biot described a pattern of irregular, or ataxic, breathing depicted in figure 1. Although widely recognized as a manifestation of opioids' toxic effects on the central respiratory pattern generator[15], the degree of ataxic breathing is not routinely monitored, in part because ataxic breathing is not currently easy to quantify in real-time. A visual scoring template for rating ataxic breathing has been suggested, but requires considerable expertise and manual offline analysis[16].

We hypothesized that a machine learning algorithm could accurately reproduce expert consensus on ataxic breathing severity in patients receiving opioids.

We suggest that monitoring for ataxic breathing could provide caretakers with critical information regarding the respiratory status of a patient, potentially in advance of life threatening adverse events.

METHODS

Informed written consent was obtained from 26 volunteers (13 male, 13 female). Eligible volunteers had an ASA physical status of I or II, age 18 to 55 years, body mass index between 18 and 30 kg/m2, negative drug screen, and uncomplicated airway anatomy. Volunteers were not eligible if they had a history of significant alcohol or drug abuse, a positive drug-screening test, allergy to opioids or propofol, obstructive sleep apnea, any prescription medication intake other than oral contraceptives in the 48 hours preceding the study, or medical illnesses that are known to alter the pharmacokinetics or pharmacodynamics of opioids or intravenous anesthetics.

Volunteer subjects were instrumented with a three lead electrocardiogram that detects respiratory rate using chest impedance (Datex Ohmeda, GE Healthcare, Helsinki, Finland), a photo-plethysmography (PPG) sensor (SET, Masimo Corporation, Irvine, CA), an abdominal accelerometer sensor (ADXL345, Analog Devices, Norwood, MA), respiratory inductance plethysmography (RIP) chest bands (Q-RIP, Braebon Medical Corporation, Kanata, ON, Canada), a capnometer nasal cannula (LoFlo, Philips Medical, Wallingford CT), a nasal airway pressure sensor (1 INCH-D-4V, All Sensors, Morgan Hill, CA), a nasal/oral thermistor (Disposable Adult Airflow Sensor, Braebon

Medical Corporation, Kanata, ON, Canada), and a peri-tracheal microphone (Audio-Technica ATR3350iS. Machida, Tokio, Japan) positioned within a metal pre-cordial stethoscope cup (Wenger #00-390-c, AINcA, San Marcos, CA) placed just below the larynx and above the suprasternal notch. Data waveforms were digitized at 100 Hz with the exception of the acoustic waveform which was digitized at 44.1 kHz. The placement of these sensors is illustrated in figure 2.

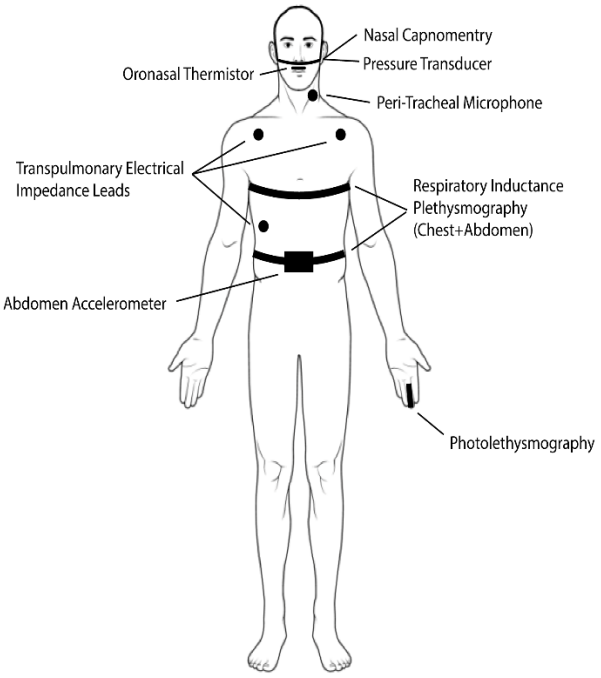

Figure 2: Placement of body sensors during study.

A 20 gauge venous catheter was placed in an antecubital vein under local anesthesia (0.2 mL of 0.5% lidocaine) for the purpose of hydration and drug administration. The IV site was similar in all subjects. A maintenance infusion of 0.9% sodium chloride was administered at 1 ml/kg/hour throughout the study. Continuous infusions of Remifentanil and Propofol was infused into this peripheral IV.

Our team previously characterized various effects of sedatives combined with opioids using drug interaction models. Specifically, we characterized the interaction of Propofol and Remifentanil on metrics of airway obstruction and intolerable ventilatory depression in volunteers.[10] Each subject received Propofol and Remifentanil. Similar to previously collected data from our volunteer laboratory (Kern et al, 2004), each drug was administered using a computer controlled (Stanpump[13]) continuous infusion pump (Pump 22; Harvard Apparatus, Limited, Holliston, MA) to achieve selected target effect site concentrations. The effect site concentration refers to the drug concentration at the pharmacologic site of action. Pharmacokinetic parameters published by Minto *et al.*[14] and Schnider et al.[15] was used for Remifentanil and Propofol respectively.

We administered Propofol and Remifentanil pairs in a dose escalation scheme with small steps in order to creep up to the desired target effects of respiratory depression, airway obstruction and both effects while avoiding overshoot. To accomplish this, the Propofol was dosed in a range of 0.75 - 4 mcg/mL in dose escalation steps of approximately 0.5 mcg/mL. Remifentanil was dosed in a range of 0.75 to 4.0 ng/mL in escalation steps of approximately 0.25-0.5 ng/mL.

Data were isolated from periods during which the patient was unperturbed, not talking, and breathing normally (no obstruction present). A custom algorithm which detects peak prominence in each signal and compares it to predefined thresholds was used to detect breathing in each signal.

The data were divided into sections containing thirty breaths each. In each section, all available sensors were plotted as waveforms to present to the domain experts. The three domain experts then individually rated each section for ataxic breathing severity according to a previously published visual scoring guideline. This guideline is presented in figure 3. The scoring guideline was digitized to 0 (no ataxia), 1 (mild ataxia), 2 (moderate ataxia), 3 (severe ataxia), and 4 (clustered breathing).

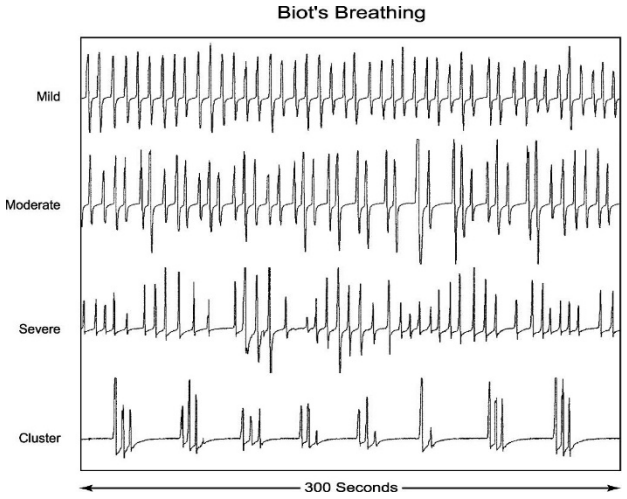

Figure 3: Ataxic breathing severity guidelines published by Farney et al[16].

The results from the raters were collected and then used to train a machine learning algorithm which used features based on interbreath interval variability and tidal volume variability to assess the degree of ataxic breathing in the data. In this case, the selected machine learning algorithm was a support vector machine using a fine guassian kernel function which was trained in Matlab.

The machine then rated a subset (test set) of the data which it had previously not been exposed to. Interrator reliability analyses were used to determine the level of concordance between the algorithm and the domain experts.

Specifically, Krippendorff's Alpha and Vanbelle's Kappa were used for this analaysis. Krippendorff's Alpha is an interrator reliability tool which attempts to rate the amount of agreement among multiple raters. A score of 0 would indicate that the raters in the set did not agree above the level you would expect to happen by chance. A score of 1 indicates perfect agreement amongst all raters in the group.

Vanbelle's Kappa expands on this calculation by attempting to isolate a single rater, in this case the machine learning algorithm, and compare it against a set of raters.

Confidence intervals on selected statistical variables were obtained by repeating the analysis 1000 times and selecting the 2.5 and 97.5 quantiles of data.

Support vector machines were trained on both RIP and nasal pressure based breath marks and tidal volumes.

RESULTS

A total of 219 30-breath segments of data fit the criteria described in the methods. On average, 100 of these segments were included in the machine learning training set and 119 were included in the machine learning testing set.

Krippendorff's alpha and Vanbelle's kappa and their confidence intervals for each respective support vector machine are reported in table 1.

Rater Statistic	RIP Band Mean (95% CI)	Intranasal Pressure Mean (95% CI)
Krippendorff's Alpha	0.912 (0.852 - 0.949)	0.899 (0.819 - 0.941)
Vanbelle's Kappa	0.970 (0.951 - 0.983)	0.961 (0.921 - 0.979)

Table 1: Interrater reliability statistics for each of the tested machine learning classifiers

DISCUSSION

Current standards of respiratory monitoring are limited in their usefulness. As an example, pulse oximetry may take as many as 2-3 minutes to report a change in blood oxygenation following cessation of breathing. While a continuous respiratory monitor may alleviate this problem, respiratory rate alone has shortcomings. For example, the number of breaths in a given interval (usually 60 seconds, but sometimes less) tells you nothing about the respiratory pattern. As an example, see figure 4. In this figure, we see respiratory waveforms recorded over roughly one minute of respiration. During this period, roughly 12 breath attempts can be seen which would normally be considered a healthy respiratory rate of 12 breaths per minute. However, we can also see that this patient experienced a long central apnea and potential airway obstruction indicated by the cessation in breathing and the out of phase RIP signals respectively.

Based upon in vitro and in vivo animal models, the genesis of opioid-induced irregular respiratory rhythm appears to rest on the differential opioid sensitivity of two anatomically distinct but coupled rhythm generators located in the rostral ventrolateral medulla[17-19]. The pre-Bötzinger complex (preBötC) and the retrotrapezoid/parafacial respiratory group (RTN/pFRG) have been posited to be essential and sufficient for generation of respiratory rhythm[17-19]. Opiate sensitive neurons in the preBötC are active during inspiration while opiate *in*sensitive neurons in the RTN/pFRG are active during expiration. Application of u-opioid receptor agonists or neurotoxic lesioning of preBötC neurons expressing neurokinin-1 receptor, results in slowing of the respiratory rate and ultimately ataxic or quantal breathing[20]. The impact of opioid agonists on u-opioid receptors in the carotid body, which appears to modulate breath by breath variability, is unclear. The inter-breath interval is the primary regulated variable responsible for physiologic conditions that cause erratic breathing[21].

Despite widespread recognition that opioid induced ataxic breathing can be an indicator of opioid toxicity in patients receiving analgesic care, it is currently not monitored due to the lack of standards regarding its measurement.

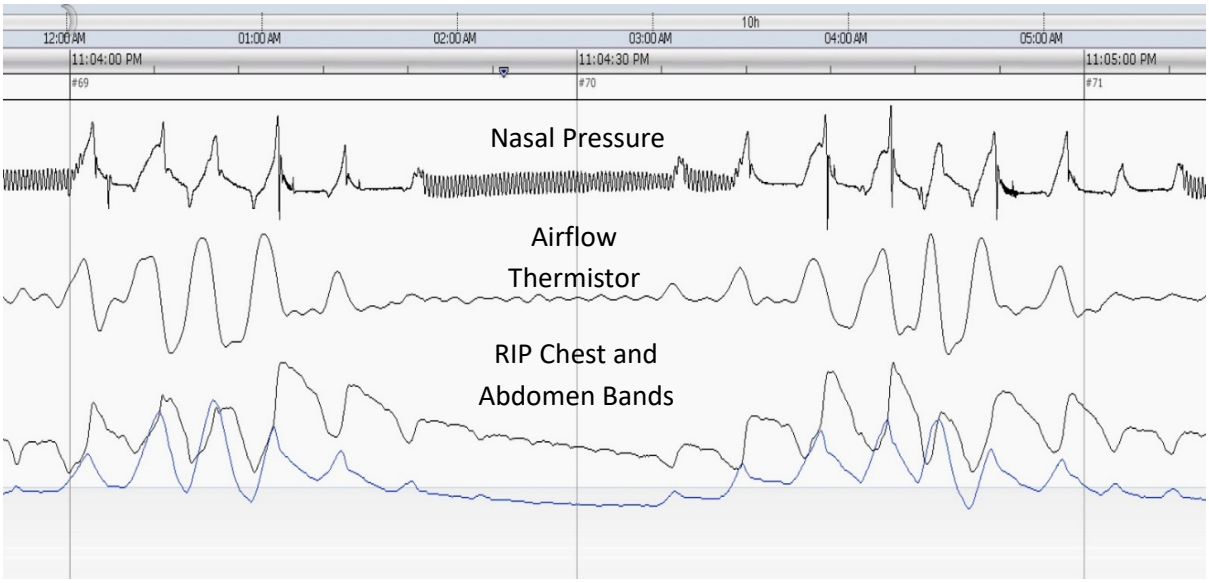

Figure 4: Three respiratory waveforms recorded over the course of sixty seconds. The middle section indicates a central apnea. Paradoxical movement in the RIP chest and abdomen bands in the latter half indicates a potential airway obstruction

The machine learning classifier created during this study was able to replicate domain expert's opinion on ataxic breathing severity with a high degree of accuracy. Interestingly, it was able to do so regardless of the underlying sensor (RIP or nasal pressure) which was used to train the algorithm. This indicates any respiratory monitor with a sufficient degree of accuracy could be trained to detect ataxic breathing severity.

It is our belief that an ataxic breathing severity score could add critical information when used in conjunction with standard respiration measures such as respiratory rate and blood oxygen saturation. The degree of breathing irregularity could be used as an indicator of opioids toxic effects on the brains respiratory pattern generators. This indication could be used to advise opioid dosing and further monitoring.

ACKNOWLEDGEMENTS

I would like to thank the Rocky Mountain Space Grant Consortium for providing funding in order to pursue this research.

I would also like to thank those individuals who are currently assisting not only in data collection and planning but also in general advice during this study. Those individuals are Soeren Hoehne, Kelly Smith, Ken Johnson, and Julia White.

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